UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/516,310	03/01/2000	Yao-Zhong Lin	22000.0021U2	3622

23859 7590 06/13/2005

NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/516,310	LIN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9-26 and 33* is/are pending in the application.

4a) Of the above claim(s) *16-26 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0

DETAILED ACTION

This Office Action is a reply to the Paper filed 21 March 2005 in response to the Non-Final Office Action mailed 17 September 2004. Claims 16-26 and 33 had been withdrawn from consideration and claims 6 and 9-15 were considered in the 17 September Office Action. No amendments were filed in the 21 March Paper. Claims 6, 9-26 and 33 are pending and claims 6 and 9-15 are under consideration.

Response to Arguments

Rejections under 35 U.S.C. §112, first paragraph, (enablement):

Claims 6 and 9-15 stand rejected under 35 USC 112, first paragraph, for lack of enablement for reasons of record and herein below in the response to arguments.

First, Office Action maintains that, given that the claims are directed to methods of using widely divergent biologically active molecules the teachings of the specification and showings of the Declaration do not support enablement for the full scope of the claimed subject matter.

In response, Applicant contends that, because the claims are not limited to targeting the complex or preventing importation of the molecule into all cells the Examiner cannot require enablement for this limitation. Applicant urges that the Declaration of Dr. Hawiger and "the examples in the specification wherein the claimed invention has been reduced to practice, one of skill in the art would have been able to make and use the invention as claimed" (paragraph bridging pages 5-6). Applicant further contends that avoiding systemic importation into all cells is *not* critical to the invention and the specification provides no teachings that would indicate that

it is critical. Applicant supports this statement with generic statements from the specification asserting that various routes of systemic or localized administration are contemplated.

These arguments have been fully considered but are not deemed persuasive. Applicant is correct to point out that the test of enablement is "whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" (emphasis added). With regard to using the claimed invention the specification teaches at page 19, lines 10-12, "*In vivo*, the method can be used to deliver into cells therapeutic molecules such as peptides and proteins to regulate aberrant functions or supply deficient cells..." Thus, the specification clearly teaches that the method is to be used therapeutically to regulate aberrant functions or supply deficient cells. The question at hand, therefore, is whether the disclosure provides sufficient direction to enable the skilled artisan to practice (make) a therapeutic method commensurate with the broad scope of what is presently claimed. The paragraph from the MPEP cited by Applicant goes on to state, "[t]he standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)." Among the factors set forth in *In re Wands* with regard to analyzing whether claims are enabled are the breadth of the claims; the state of the prior art; the amount of direction provided by the inventor; the existence of working examples; the relative skill of those in the art; whether the quantity of experimentation needed to make or use the

invention based on the content of the disclosure is "undue"; and the level of predictability in the art.

In the instant case, the claims are extraordinarily broad because they embrace a method of delivering essentially any peptide, polypeptide or protein into any cell in any subject and the specification teaches that the method is to be used to deliver into cells therapeutic molecules to regulate aberrant functions or supply deficient cells. The art discussed in the previous Office Action (beginning at page 5) clearly demonstrates that delivery of molecules into cells in subjects using importation competent signal peptides remained at an early stage of development nearly 10 years after the effective filing date of the instant application and recognizes that targeting is an important aspect remaining to be addressed before useful methods of importing a peptide, polypeptide, or protein into a cell in a subject are generally enabled.

To summarize, Kabouridis teaches, "a major disadvantage [of using translocating peptides] is lack of targeting specificity. Therefore, for each case, it will be important to establish not only that the PTD-chimera has beneficial effect on diseased cells but also that it has no adverse effects on healthy tissue" (first full paragraph on page 502). Schwarze *et al.* concurs with the teachings of Kabouridis, stating, "[a]n effective drug must be active only in the diseased cell. As translocating proteins can readily enter all cell types, specificity must be built into the molecule" (second full paragraph on page 294).

Although, as Applicant points out, the claims are not limited to targeting the administered complex and the specification expresses no concern with regard to avoiding delivery of the complex to all cells in a subject, the teachings of Kabouridis and Schwarze *et al.* clearly demonstrate that targeting is an important concern in developing a method, such as the one

presently claimed, that is to be used to deliver into cells therapeutic molecules such as peptides and proteins to regulate aberrant functions or supply deficient cells. Thus, the usefulness of any given method of delivering a peptide, polypeptide or protein into a cell in a subject will have to be determined on a case by case basis by empirical experimentation, at least because the effects of an untargeted peptide, polypeptide or protein on the organism as a whole is unpredictable.

Furthermore, the art cited in the previous Office Action goes on to teach additional sources of unpredictability including immunogenicity of the translocating peptide itself or its cargo and the absence of basic pharmacological information such as tissue distribution, protein half-life and effective modes of delivery. The teachings of Kabouridis and Schwarze *et al.* indicate that, even years after the effective filing date of the instant application, many basic questions regarding the effective use of translocating peptides *in vivo* remained to be answered. These aspects of developing the method such that it is generally enabled for useful importation of any peptide, polypeptide or protein into any cell in any subject are not addressed in Applicant's arguments.

Contrary to Applicant's assertion the instant specification does not contain a single working example of the invention now claimed. The working examples provided are limited to *in vitro* and do not address the issues raised by Kabouridis and Schwarze *et al.* Furthermore, given that the claims are directed to methods of using widely divergent biologically active molecules, the showings of the Declaration, which are limited a single species of importation competent signal peptide with a single species of peptide do not support enablement for the broad scope of the claimed subject matter.

With regard to toxin polypeptides, which were provided as an example of embodiments within the scope of the claims that would require targeting for use in the method claimed, Applicant contends that evidence of safety in treatment of humans or regarding the degree of effectiveness is not the concern of the Patent Office. In response, the Examiner has not requested evidence of safety in the treatment of humans and has not rejected the claims as lacking utility, which is what the statements cited by Applicant address. Instead, the Examiner contends that the field of the invention is highly unpredictable and that developing the method such that it can be used as broadly claimed would require undue experimentation. The delivery of toxic proteins into a cell in a subject poses significant technical challenges, such as global toxicity, which would hinder the development of a useful method and which must be addressed in order to use the full scope of what is presently claimed. As pointed out by Applicant, in spite of the teachings of the art to the contrary, the instant application does not view issues such as targeting as critical to practicing the method and provides no teachings that would enable the skilled artisan to develop the claimed method such that it could be used as broadly claimed without undue experimentation.

In the previous Office Action, the Examiner contends that another aspect of the claimed method which must be addressed on a case-by-case basis is the operability of the cargo delivered by importation competent signal peptide. The specification teaches, "[n]aturally, only those molecules which are of a size which can be imported into the cell are within the scope of the invention. However, since very large proteins (ranging form molecular weights of about 100,000 to around 1 million) are exported by cells (*e.g.*, antibodies, fibrinogen, and macroglobulin), very large proteins can be imported into cells by this method" (page 6). The Office Action contends

that the accuracy of this assumption clearly requires that the mechanism by which these large proteins are exported is the same as the mechanism by which hydrophobic importation competent signal peptides import proteins.

In response, Applicant asserts that the molecules imported by the claimed methods pass through the membrane which is entirely analogous to proteins with signal peptides crossing the endoplasmic reticulum (ER) membrane. Applicant states, "[t]he claimed signal peptides allow transport across a membrane (cell membrane or ER membrane) and, as it is know form [sic] the many proteins transported across the ER membrane, a wide size rage of proteins can be so transported" (page 7).

By this, Applicant appears to be asserting that the plasma membrane of the cell and the ER membrane are essentially the same and that any mechanism of protein transport that exists in the ER membrane must also be present in the plasma membrane. This is a fundamental misconception. For example, the specification cites fibrinogen as an example of a large protein exported by cells. Redman *et al.* (2001) *Ann. NY Acad. Sci.* 936:480-495 teaches that in biosynthesis, "[t]he nascent fibrinogen chains, each on separate polysomes, are cotranslationally directed towards the lumen of the ER..." What is meant by this is described in the following passage from Agarraberes *et al.* (2001) *Biochim. Biophys. Acta* 1513:1-24 (citations omitted, emphasis added):

> In eukaryotic cells the majority of polypeptides destined to cross the ER membrane are translated and translocated simultaneously. In addition to resident ER proteins, many proteins destined for secretion or for residence in the plasma membrane, the Golgi apparatus, lysosomes, and the endosomal compartments also enter the ER lumen cotranslationally []. Proteins targeted to the ER are synthesized with a signal sequence usually in the amino-terminal region similar to the sequence described for bacterial proteins utilizing the Sec pathway [] (Fig. 4). The SRP binds both to the signal sequence in the nascent polypeptide and the translating ribosome and targets the complex to the ER membrane [] (Fig. 4). Binding of the SRP to the translating ribosome results in slowing of translation [].

> The signal recognition particle consists of a complex of six polypeptides and one molecule of RNA []. The 54 kDa subunit of the SRP is responsible for binding to the signal sequence, and this interaction increases the SRP's affinity for GTP []. The SRP binds to its receptor (SRp/SRp) on the surface of the ER, and the ribosome binds to the translocation site on the ER membrane []. The interaction between the SRP and SRp induces the hydrolysis of GTP []. As a consequence, the SRP is released into the cytosol, the ribosome binds to the ER membrane, and the nascent polypeptide is transferred into the aqueous channel of the translocon [].
>
> The ribosome binds tightly to the Sec61p complex in the ER membrane []. The Sec61p complex consists of three polypeptides, Sec61p, Sec61p, and Sec61p (Fig. 4). This protein complex is responsible for the formation of the aqueous channel and the initial recognition of the signal sequence during the insertion of the nascent polypeptide into the translocon []. Interestingly, Sec61p and Sec61p are the eukaryotic homologues of bacterial SecYp and SecEp, respectively []. The translocating chain-associated membrane (TRAM) protein preferentially interacts with the signal sequence of most of the proteins translocated during the early stages of protein translocation [] but its exact function in protein translocation is not clear. The SR, the Sec61p complex, and the TRAM protein constitute the minimal requirement for reconstitution of protein translocation in liposomes [].

Thus, the art teaches that most polypeptides, including fibrinogen, cross the ER membrane via a complex process that involves synthesis of the protein. It would seem extraordinarily unlikely that the process that enables fibrinogen to cross the ER membrane is operative at the plasma membrane and, at any rate, would not be the mechanism by which the instant peptide, polypeptide or protein is delivered into a cell since it is already in the form of a protein and would not be newly synthesized during transport. Although Agarraberes teaches that some proteins are also transported into the ER by a posttranslational mechanism that is less well understood, this process is also thought to involve a cytoplasmic complex of molecular chaperones and a complex of ER proteins such as Sec62p, Sec71p,and Sec72p as well as ER luminal proteins required to pull the substrate protein into the ER lumen concomitant with ATP hydrolysis (see especially Figure 5 and the caption thereto and the discussion bridging the left and right columns on page 8). Again, it is highly unlikely that this complicated process involving cytosolic, ER membrane and ER luminal protein complexes would be the operative process in

transporting peptides, polypeptides or proteins across the plasma membrane in the instant method. Thus, the skilled artisan would not have viewed protein transport into the ER as a valid model of protein transport across the plasma membrane as required by the method presently claimed.

In the first full paragraph on page 8, Applicant asserts that the plasma membrane can be bypassed with the use of a signal sequence, which allows for importation of biologically active molecules. In response to the Examiner's contention that the skilled artisan would not expect that the ability of a hydrophobic importation fusion protein to cross the plasma membrane to be independent of the cargo, Applicant contends that the fusion protein does not cross the plasma membrane independently of the cargo peptide, but rather allows for its importation into the cell.

It would seem that Applicant has misunderstood the Examiner's position. As stated above, the skilled artisan would not expect that the ability of a hydrophobic importation fusion protein to cross the plasma membrane to be independent of the cargo. What is meant by this is that the skilled artisan would expect that the properties of the cargo would have some significant impact on whether the complex as a whole would cross the plasma membrane. For example, in discussing possible mechanisms for polypeptide translocation across the ER membrane by the posttranslational mechanism discussed above, Liebermeister *et al.* (2001) *J. Mol. Biol.* 305:643-656 teaches, "it is intuitively clear that too tightly folded a polypeptide chain cannot be transported by a Brownian ratcheting mechanism, but how folded can the polypeptide be? Similarly, if hydrophobic segments of a polypeptide chain can laterally exit the channel into the lipid phase, what is the maximum hydrophobicity up to which translocation of a secretory protein would not be perturbed?" (paragraph bridging the left and right columns on page 644).

Thus, even if one has some idea as to the mechanism by which a polypeptide is translocated across a membrane, one does not expect that all proteins can be translocated by that mechanism and it is difficult to predict which can and which cannot.

In the instant case, although the mechanism by which the hydrophobic importation competent signal peptides cross the plasma membrane is unknown, given what is known about the unpredictability of protein translocation across membranes, the skilled artisan would not expect that the hydrophobic importation competent signal peptide of the instant claims would be capable of importing any peptide, polypeptide or protein into any cell in a subject. Therefore, the skilled artisan would have to resort to empirical experimentation to identify which embodiments within the scope of the claims are operative.

With regard to Namiki *et al.*, discussed in the second full paragraph of Applicant's response, the paper was cited because the Examiner could find only a single example of a large protein being transported across the plasma membrane via a signal-sequence-based peptide (*i.e.*, GST). However, Namiki *et al.* demonstrated that the signal-sequence-based peptide was not necessary for transport of GST. Therefore, the teachings of Namiki *et al.* discredit the only example of a cargo larger than a small peptide being translocated according to the method of the instant claims.

With regard to the Examiner's contention that the teachings from the art and specification do not provide sufficient guidance with regard to which cargo proteins, peptides or polypeptides can be delivered into a cell *in vivo*. Applicant asserts that the statement, "Therefore, size ranges for proteins from a few amino acids to around a thousand amino acids can be used. A preferable size range for proteins is from a few amino acids to about 250 amino acids", provides

the means to use the invention. However, this teaching, and the teachings of the specification as a whole, fail to identify which embodiments within the broad generic ranges recited would actually be operative in the method. Therefore, the skilled artisan would have to resort to undue trial and error experimentation to identify the operative embodiments within the scope of the claims.

Next, Applicant cites a passage from the MPEP which states, "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." Applicant contends that the teachings of Lindgren *et al.* and Namiki *et al.*, cited in the previous Office Action as teaching that cell-penetrating peptides were not known in the art for large cargoes, are not relevant because the instant invention uses hydrophobic importation signal peptides that were not known in the art at the time of the invention.

This argument is not persuasive. As described in the previous Office Action and herein above, the skilled artisan would not expect that importation competent signal peptides of the instant claims would be capable of delivering any peptide, polypeptide or protein into a cell in a subject as claimed given the complexities of protein translocation across membranes and the absence of any evidence that protein translocation is independent of the properties of the protein translocated, such as size, hydrophobicity and tightness of folding. Therefore, adequate reasons have been advanced by the Examiner to establish that a person could not use the genus as a whole without undue experimentation. The disclosure of the instant application was published as US Patent No. 5,807,746 on 15 September 1998, two years before Lindgren *et al.* was published.

However, to this date there is no example of a large protein being translocated into a cell in a subject by a method involving a mammalian hydrophobic importation competent signal peptide.

Finally, Applicant contends that the disclosure is enabling for the broad scope of any mammalian hydrophobic importation competent signal peptide because one of skill in the art because not every peptide having the structural features of a hydrophobic importation competent signal peptide would need to be assayed for activity because the specification teaches, "Signal peptides can be selected, for example, from the SIGPEP database, which also lists the origin of the signal peptide. When a specific cell type is to be targeted, a signal peptide used by that cell type can be chosen." Applicant urges that the SIGPEP database could have been used to make and use the invention as claimed and further argues that the selected signal peptide could be tested for its ability to function as an importation competent signal peptide using routine screening methods.

This argument has been fully considered but is not deemed persuasive. An "importation competent signal peptide" is defined in the paragraph bridging pages 10-11 of the specification as "a sequence of amino acids generally of a length of about 10 to 50 or more amino acid residues, many (typically about 55-60%) residues of which are hydrophobic such that they have a hydrophobic, lipid-soluble portion" and "[t]he signal peptides of this invention, as discovered herein, are also 'importation competent,' i.e., capable of penetrating through the cell membrane from outside the cell to the interior of the cell." Although the SIGPEP database might be used as a starting point to identify some embodiments within the scope of the claims, the importation competent signal peptide of the claims clearly encompasses any sequence of amino acids generally of a length of about 10 to 50 or more amino acid residues and that is 'importation

competent. As the importation competent signal peptide is in no way limited to those that might be found in the SIGPEP database, the skilled artisan seeking to practice the invention in accordance with the full scope of the claims would not be able to confine the search to those peptides disclosed in the SIGPEP database. As stated in the previous Office Action, given the tremendous scope of the claims and the absence of teachings that would enable the skilled artisan to identify those peptides having the function of an importation competent signal peptide, determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is normally required in the art. Therefore, practicing the full scope of the claimed method would require undue experimentation.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure.

Rejections under 35 U.S.C. §112, first paragraph, (possession):

Claims 6, 10, 11 and 13-15 stand rejected under 35 USC 112, first paragraph for insufficient written description for reasons of record and herein below.

The previous Office Action asserts that a recitation of functional characteristics alone does not provide adequate written description for a molecule but must be coupled with a known or disclosed correlation between function and structure. To evidence the inadequacy of the instant disclosure, the Office Action cites Applicant's own teachings in Veach *et al.* wherein the authors report studies aimed at analyzing the mechanism of hydrophobic importation polypeptide translocation for the stated purpose of facilitating the rational design of a new generation of cell-

permeant peptides (first full paragraph on page 11426). The Examiner notes that in the publication Applicant suggests that there is a proline residue comprised within hydrophobic importation polypeptides that is critical to their ability to cross the plasma membrane that is not disclosed instant disclosure.

In response Applicant contends that Veach *et al.* did not construe the presence of the proline as being critical and simply stated that the hydrophobic region contained a proline, and stated that the presence of proline may allow SSHR to form a hairpin-like loop that constitutes a leading edge for the attached cargo. Applicant points out that Veach *et al.* goes on to postulate another reason for the ability of SSHR to pass through the phospholipids bilayer: a "tilted peptide translocation". Applicant also cites a 1996 publication (Liu *et al.*) which discloses a cell permeable peptide designed using a signal peptide sequence of human β3 integrin, which does not contain a proline residue. Based on this Applicant concludes, characterization of the proline residue as necessary is unfounded.

These arguments are not deemed persuasive. The statement from Veach *et al.* suggests that the proline may allow the SSHR to form. As the SSHR is required in either mechanism for SSHR-based translocation, formation of the SSHR and hence the proline, which is postulated to allow the SSHR to form, is critical to the function of the importation competent signal peptide. Applicant's contention, based on the teachings of Liu *et al.*, that Veach *et al.* may be mistaken in the identification of the proline as a possible structural determinant of importation competent signal peptides only serves to further illustrate the absence of any clear nexus of structure and function even ten years after the effective filing date of the instant application.

Next, Applicant reiterates the argument that a description of a process need only provide a description of the act to be performed. These arguments were addressed in the previous Office Action. To summarize, it is the Examiner's position that a description of a method of using an importation competent signal peptide must describe that which is being used in the method. Applicant seems to be arguing that a method of delivering a biologically active molecule into a cell need not describe the active agent used in delivering said biologically active molecule; that a recitation of function in the context of a positive process step meets the written description requirement of 35 U.S.C. §112, first paragraph. By this reasoning, a claim to a method of curing cancer comprising administering an agent that cures cancer also meets the written description requirement.

Applicant argues that nothing in the statute or the case law requires a written description of anything other than the claimed invention for compliance with the written description requirement. While the Examiner accepts this general premise, there is nothing to suggest that a description of the materials used in a method is irrelevant to the description of the method itself. In contrast, it is the Examiner's position that claims directed to a method of delivering an agent are not adequately described if the skilled artisan could not envision what is being delivered. This is supported by the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, first paragraph, 'Written Description' Requirement" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices), which state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed

invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966; emphasis added).

Applicant argues that the requirement that the manner and process of making and using the claimed invention be described is not part of the written description requirement. Applicant discussed the case law establishing that the written description requirement of 35 U.S.C. §112, first paragraph, is distinct from the enablement requirement, which is acknowledged by the Examiner. However, the Examiner maintains that a description of a method of using a product must describe the product being used in order to meet the written description requirement. The claims recite a single process step (i.e., administering to the subject...). Applicant seems to be arguing that the invention is adequately described, even if the importation competent signal peptide is not, because the specification describes the act of administering. However, it is the structure of the importation competent signal peptide itself, not administering, that dictates importation of the biologically active molecule. Surely it cannot be the case that a description of a method of delivering a bioactive molecule into a cell need not describe that which actually delivers the bioactive molecule into a cell.

Applicant asserts that identification of additional importation competent signal peptides does not implicate the requirements of written description. Applicant argues, "the claim requires that the peptide, polypeptide, or protein be imported into the cell of the subject. This is an effect of the method, not a step of the method. Obtaining this effect is solely an issue of enablement, not written description. The effect is not a step or act required to perform the method, it is only a result that those of skill in the art must be able to obtain" (page 14). However, it is the Examiner's position that the step or act of administering is not fully described without a

description of what is being administered. The claim is directed to a method of importing a biologically active molecule into a cell in a subject. Applicant is arguing that a description of the act of administering adequately describes this method even though the act itself is generic to all methods of treatment and, in and of itself, does not generally result in importation of a biologically active molecule into a cell. It is unclear how merely describing an action that does not result in a biologically active molecule being imported into a cell fully describes a method of importing a biologically active molecule into a cell. Applicant further argues, "how to make the importation competent signal peptides is at most only an aspect of how to 'make' the claimed method because the materials to be used in a method are arguably part of 'making' such a method. Making the materials used in a claimed method is clearly not the method itself or a step in the method" (page 15). This argument was not found persuasive because the basis for the written description rejection is that the specification does not describe the importation competent signal peptide of the claims (the "how to make" requirement has been addressed in previous Office Actions and herein above with regard to enablement under 35 U.S.C. §112, first paragraph). For reasons also provided in previous Office Actions and herein above, the claimed method of using an importation competent signal peptide as a whole is not adequately described in the absence of a description of the importation competent signal peptide itself.

In response to these Arguments, Applicant asserts that the broad scope of the importation competent signal peptide of the claims is adequately described by the example of the SN50 peptide and the teaching that signal peptides can be selected, for example, from the SIGPEP database. However, as discussed herein above, an "importation competent signal peptide" is defined in the paragraph bridging pages 10-11 of the specification as "a sequence of amino acids

generally of a length of about 10 to 50 or more amino acid residues, many (typically about 55-60%) residues of which are hydrophobic such that they have a hydrophobic, lipid-soluble portion" and "[t]he signal peptides of this invention, as discovered herein, are also 'importation competent,' i.e., capable of penetrating through the cell membrane from outside the cell to the interior of the cell." The peptides disclosed in the SIGPEP database do not serve as species of the claimed invention unless it is Applicant's contention that all peptides disclosed in that database have the function of an importation competent signal peptide. In contrast, the teachings of the specification would appear to suggest that the SIGPEP database is generic to peptides that might or might not have the function of an importation competent signal peptide and the skilled artisan might identify importation competent signal peptides within that genus by empirical experimentation. Thus, the application provides only one species of an importation competent signal peptide and a suggestion of where one might search for additional importation competent signal peptides. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004). Given the broad structural features contemplated in the application and the absence of any established correlation of structure with function, the single

disclosed species clearly fails to describe the generic importation competent signal peptide of the claims.

Furthermore, an adequate written description of a peptide requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the peptide itself. It is not sufficient to define DNA solely by its principal biological property (*i.e.*, it is an importation competent peptide), because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any peptide with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all peptides that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Finally, Applicant argues that the signal peptides of the instant claims are not new or unknown biological materials that the ordinary skilled artisan would easily miscomprehend and are therefore, like the cells of *Amgen*, well known biological materials. Thus, Applicant appears to be arguing that at the time the invention was made (*i.e.*, prior to 1994), importation competent signal peptides were conventional in the art. This assertion would seem to be at odds with Applicant's previous assertion (in the first full paragraph on page 9 of the "Remarks") that that the teachings of Lindgren *et al.*, published in 1998, are not relevant to the instant claims because the instant invention uses hydrophobic importation signal peptides that were not known in the art at the time of the invention. Given the absence of any art disclosing mammalian importation

competent signal peptides prior to the effective filing date of the instant application, the skilled artisan would not have viewed the importation competent signal peptide of the claims as conventional in the art at the time the invention was made. The record as a whole clearly establishes that the importation competent signal peptide of the claims were not well-defined at the time the instant application was filed and, therefore, the skilled artisan would not have viewed the teachings of the specification as demonstrating that Applicant was in possession of the full scope of what is now claimed.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636